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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Shizuo Akira

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EXAMINER

HAMA, JOANNE

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1632

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/573,212	Applicant(s) AKIRA ET AL.	
	Examiner JOANNE HAMA	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 February 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>3/7/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant filed a response to the Non-Final Action of November 1, 2007 on February 1, 2008. Claims 1-5 are amended. Claims 6-8 are new.

Claims 1-8 are under consideration.

Information Disclosure Statement

Applicant filed an Information Disclosure Statement (IDS) on March 7, 2008. The IDS has been considered.

Withdrawn Rejection/Objection

Claim Objection

Applicant's arguments, see page 4 of Applicant's response, filed February 1, 2008, with respect to the objection of claims 4 and 5 have been fully considered and are persuasive. Applicant indicates that the claims have been amended such that they are not multiply dependent on another multiple dependent claim. The objection of claims 4 and 5 has been withdrawn and claims 4 and 5 are now under consideration.

New/Maintained Rejections

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-3 remain rejected and claims 4-8 are newly rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility, for reasons of record, November 1, 2007.

Applicant's arguments filed February 1, 2008 have been fully considered but they are not persuasive.

Applicant indicates that the Examiner has incorrectly applied the requirements of 35 USC § 101 to the present claims. It is not Applicant's burden to establish utility unless the Examiner shifts the burden by establishing, with evidence, that one of skill in the art would doubt the asserted utility (Applicant's response, page 4). With regard to the Examiner indicating that in regards to asserted utility 2)...the specification fails to demonstrate that mice with a homozygous disruption of an endogenous TRAM gene have any phenotype associated with any disease, or can in fact be used as a model for any particular disease (Office Action, November 1, 2007, page 5), Applicant directs the Examiner's attention to the passage excerpted from pages 5-7 of the specification. Applicant indicates from the specification that TRAM-deficient mice showed severe defects in cytokine production, splenocyte proliferation and up-regulation of surface molecules in response to TLR4 ligands, but not to other TLR ligands. Further, expression of IFN-beta and IFN-inducible genes was inhibited in TRAM-deficient mice. In TRAM-deficient mice, TLR4-mediated production of proinflammatory cytokines was reduced. In addition to this, TRAM-deficient mice had severely defective MyD88-dependent responses to the ligands recognized by TLR4. Furthermore, activation of the TLR4-mediated MyD88-independent, but not MyD88-dependent signaling cascade was

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abolished in TRAM-deficient mice. TRAM-deficient mice showed a normal response to TLR3 ligands (Applicant's response, pages 5-7). In response, this is not persuasive. While Applicant indicates the phenotypes that TRAM-deficient mice exhibit, neither the specification nor the art indicates what these symptoms are a disease of. In addition to this, neither the specification nor the art indicates that there are TRAM-deficient patients who exhibit these symptoms such that the TRAM-deficient mice can be used as a model of the disease and be used in a screen for medicaments that treat a TRAM deficiency. Because neither the specification nor the art provide guidance regarding these issues, the use of the claimed mice is not readily apparent.

Applicant indicates that the USPTO's Utility Guidelines state that a patent examiner must accept a utility asserted by an applicant unless the Office has evidence or sound scientific reasoning to rebut the assertion. The Guidelines makes a similar point several pages later, stating that Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. In response, the Examiner does not doubt that the claimed mice exhibit particular characteristics as described in the specification. However, the issue of utility is raised as it is unclear what the claimed mice that exhibit these phenotypes are to be used for. As indicated above and in the previous Office Action, neither the art nor the specification indicates that the symptoms identified in the claimed mice are related to any disease or disorder such that

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the mice can be used as a model to screen for medicaments. As such, the use of the claimed mice that exhibit these phenotypes are not readily apparent.

With regard to Applicant indicating that the claimed mice can be used to test for defects in cytokine production, splenocyte proliferation, and up-regulation of surface molecules in response to TLR4 ligands, as well as how to test for inhibition of TLR4-mediated expression of IFN-beta and IFN-inducible genes (Applicant's response, page 8), these reasons are not specific and substantial uses of the claimed mice. Using the mice to identify defects in cytokine production, splenocyte proliferation, and up-regulation of surface molecules in response to TLR4 ligands and to identify TLR4-inhibited IFN-beta and IFN-inducible genes is further research that studies the properties of the claimed product itself and does not constitute substantial utility. Further, testing for defects in cytokine production, splenocyte proliferation, and up-regulation of surface molecules in response to TLR4 ligands, and testing for inhibition of TLR4-mediated expression of IFN-beta and IFN-inducible genes are not specific uses of the claimed mice because determining the biological effects caused by gene loss is a general use of any knockout mouse. As such, the claimed mice lack specific and substantial utility.

Thus, the claims are rejected.

With regard to claims 1-3 being rejected as to being directed to non-statutory subject matter, Applicant indicates that claims 1-3 have been amended to non-human

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“transgenic” animals (Applicant’s response, February 1, 2008, page 7). The rejection as it applies to this issue is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 remain rejected and claims 4-8 are newly rejected under 35 U.S.C.

112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record, November 1, 2007.

Applicant's arguments filed February 1, 2008 have been fully considered but they are not persuasive.

Applicant indicates that the Examiner states that the claimed non-human animals do not exhibit any phenotype related to any disease or disorder and thus the use of the claimed non-human animals for reason other than as a model of disease is not readily apparent (Office Action, November 1, 2007, page 7). Applicant indicates that as described above in the response to the Utility rejection, the specification clearly describes that TRAM-deficient mice showed severe defects in cytokine production and splenocyte proliferation. Applicant indicates that pages 5-7 of the specification provide guidance of these phenotypes (Applicant’s response, page 8). In response, as

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indicated above, this is not persuasive. While the specification indicates what phenotypes the TRAM-deficient mice exhibit, neither the specification nor the art provide any guidance that the symptoms exhibited by the mice are related to any disease or disorder. Because neither the specification nor the art provide any guidance as to what the mice are a model of, the use of them to screen for medicaments is not readily apparent.

Applicant indicates that that the specification provides direction to one of skill in the art as to how to generate TRAM-deficient mice and how to test for defects in cytokine production, splenocyte proliferation, and up-regulation of surface molecules in response to TLR4 ligands, as well as how to test for inhibition of TLR4-mediated expression of IFN-beta and IFN-inducible genes (Applicant's response, page 8). In response, the Examiner was not questioning how the claimed mice could be made. The issue at hand relates back to the Utility rejection, wherein the specification does not provide guidance on the specific and substantial use the claimed mice that exhibit the phenotypes described in the specification (see above). Because the specification does not provide guidance a specific and substantial use of the claimed mice, the mice are not enabled.

The Examiner had also indicated that the claims encompass the use of any ES cells from any species of non-human animal, such that any non-human comprising a disruption in TRAM is obtained. The Examiner had indicated that neither the art nor the specification provides further guidance that knockout non-human animals, using ES cells, other than mouse, are routine in the art (Office Action, November 1, 2007, pages

11-12). No response was provided by Applicant, regarding this issue. Thus, the rejection as it applies to the breadth of non-human transgenic animals remains.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-7 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 7 are unclear because the claims are drawn to products and depend on method claims. A suggested amendment to claim 6 is, "The method of claim 4, wherein the non-human animal is a mouse."

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Tuesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Joanne Hama/
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